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Current Trends for Regulatory Requirements of Elemental Impurity in Drug Substance for Regulatory Market

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ABSTRACT

The presence of elemental impurities in drug substances has gained increasing attention in the pharmaceutical industry due to their potential impact on product safety and efficacy. Regulatory agencies worldwide have established guidelines and requirements to ensure the control and mitigation of elemental impurities in drug substances and products. This review article provides a comprehensive analysis of the regulatory landscape surrounding elemental impurity control, focusing on both drug substances and the broader pharmaceutical market.

Keywords: Elemental; Drug; Impurities; Products

INTRODUCTION

Heavy metals and other trace elements are examples of elemental contaminants that can seriously jeopardize patient safety as well as the standard of pharmaceutical products [1]. The significance of limiting elemental contaminants in drug compounds is discussed in this section, along with the regulatory framework that different health authorities have created to handle this issue [2,3]. The pharmaceutical sector functions within a strict regulatory system designed to guarantee the quality, safety and efficacy of pharmaceuticals. The management of elemental contaminants in medicinal ingredients and the larger pharmaceutical industry is one crucial area that has attracted more attention recently. Heavy metals and other trace elements are examples of elemental contaminants that have the potential to jeopardize patient safety as well as the general quality of pharmaceutical formulations [4]. Global regulatory organizations have taken action to address this worry by establishing extensive rules and regulations that regulate the evaluation, management and reduction of elemental impurities at every stage of the medication development process [5]. Setting the scene, the introduction emphasizes how crucial it is to remove elemental contaminants in medications. It starts off by outlining the possible dangers connected to the presence of trace elements and heavy metals in medicinal ingredients and products. These hazards go beyond shortterm health issues; they also include the possibility of reduced therapeutic efficacy and long-term health consequences for patients. Harmonized regulatory effort s are necessary to provide consistency and uniformity in elemental impurity control standards acoss region as pharmaceutical research becomes more globally integrated [6,7]. This obligation requires a thorough comprehension of the regulatory environment surrounding elemental impurities, including directives from globally renowned organizations like the International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH), regional pharmacopeias like the European Medicines Agency (EMA) and the United States Pharmacopeia (USP), as well as other pertinent regulatory bodies [8].

LITERATURE REVIEW

Sources of contamination

Drug products and APIs can contain contaminants from a variety of sources. It comprises contaminants linked to stereochemistry, residual solvents, crystallization and synthesis intermediates and by-products. Additionally, it covers formulation, impurities that develop during storage, method-related issues, interactions between ingredients and typical degradation related to functional groups [9].

Elemental impurities in the pharmaceutical market: This section addresses the broader implications of elemental impurity management in the pharmaceutical business, extending beyond medicinal ingredients [10].

- Elemental impurities in finished drug products.
- Impact on pharmaceutical manufacturing processes.
- Considerations for combination products and medical devices.

Classification of elements

The elements covered by this guideline have been divided into three groups according to their probability of occurring in a medicinal product and their level of toxicity (PDE). The likelihood of occurrence is determined by a number of factors, such as the element's observed natural abundance and environmental distribution, its likelihood of being used in pharmaceutical processes and its likelihood of co-isolating with other elemental impurities in materials used in pharmaceutical processes. According to study, an element is considered to have a low natural abundance if its stated natural abundance is less than one atom per 106 silicon atoms. The goal of the classification system is to concentrate the risk assessment on the most hazardous components while maintaining a plausible chance of being present in the final medication [11]. The classes of elemental impurities are:

Class 1: As, Cd, Hg and Pb are human toxicants with little to no application in the production of medications. The materials that are routinely utilized to make drug products usually contain them (e.g., mined excipients). Owing to their special characteristics, these four components need to be considered in the risk assessment process, taking into account all possible administration routes and sources of elemental impurities. The results of the risk assessment will identify the aspects that might need further controls, including testing for class 1 elements in certain circumstances. Testing for class 1 elemental impurities is not anticipated to be necessary for every component; rather, testing need to be implemented only in cases where the risk assessment designates it as the suitable measure to guarantee that the PDE will be fulfilled.

Class 2: Generally speaking, substances in this class are regarded as human toxicants that depend on a pathway. Subclasses 2A and 2B of class 2 elements are further subdivided according to the proportional probability of their occurrence in the medicinal product.

- **Class 2A:** Elements are highly likely to occur in the drug product; hence, risk assessment is necessary across all possible routes of administration and sources of elemental impurities (as mentioned). Co, Ni and V are the elements of class 2A.
- **Class 2B:** Elements are rare and have little chance of co-isolating with other materials; their likelihood of occurring in the medicinal product is decreased. Therefore, unless they are included on purpose when making drug compounds, excipients or other parts of the drug product, they might not be included in the risk assessment. In class 2B, the elemental impurities include Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl.

Class 3: Although the elements in this class have large PDEs (usually greater than 500 µg/day) and are relatively lowly hazardous when administered orally, they may still need to be taken into account when assessing the danger of inhalation and parenteral routes. Unless these components are purposefully introduced, oral modes of delivery do not require their consideration in the risk assessment. Unless the PDE specific to a given route is greater than 500 µg/day, the possibility of these elemental impurities being included in parenteral and inhalation products should be assessed during the risk assessment. This class contains the following elements: Mo, Sb, Sn, Li, Ba, Cr and Cu.

Other components: This guideline does not cover several elemental impurities for which PDEs have not been defined because to their low inherent toxicity and/or variations in regional legislation. Other guidelines, regional regulations and practices that may be applicable for specific elements (e.g., Al for patients with compromised renal function; Mn and Zn for patients with compromised hepatic function) or quality considerations (e.g., presence of W impurities in therapeutic proteins) for the final drug product address these elemental impurities if they are present or included in the drug product. A few elements that are taken into consideration are Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn.

DISCUSSION

Requirements for elemental impurities in drug substances under regulation

The International Council for Harmonization of technical standards for human use pharmaceuticals (ICH): Drug products may contain elemental impurities from a variety of sources, such as residual catalysts added purposefully during synthesis or impurities arising from interactions with processing equipment, container/closure systems or drug product components. Elemental impurities have no therapeutic advantage for the patient; hence their concentration in the medication product should be kept below reasonable bounds. This guideline is divided into three sections: The assessment of toxicity data for possible elemental impurities; the creation of a Permitted Daily Exposure (PDE) for every element of toxicological concern; and the use of a riskbased strategy, as indicated in Table 1, to control elemental impurities in drug products. As long as the PDEs are not exceeded by the elemental impurities in drug products, an applicant is not expected to tighten the limitations based on process capabilities. For all patient categories, the PDEs outlined in this guideline are thought to protect the public's health. When levels of elemental impurities below toxicity criteria have been demonstrated to affect other quality features of the therapeutic product (e.g., element catalyzed degradation of drug ingredients), then lower levels of these impurities may in some situations be justified. Furthermore, from the standpoint of pharmaceutical quality, elements with high PDEs might need to be evaluated against other limitations and other criteria (such as ICH Q3A) should be examined. A platform for creating a risk-based control approach to reduce elemental contaminants in the drug product is provided by this process (Table 1).

Table 1: Permitted daily exposures for elemental impurities.

Elements	Class	Oral PDE (µg/day)	Parenteral	Inhalation
			PDE (µg/day)	PDE (µg/day)
Cadmium	1	5	2	2
Lead	1	5	5	5
Arsenic	1	15	15	2
Mercury	1	30	3	1
Cobalt	2A	50	5	3
Vanadium	2A	100	10	1
Nickel	2A	200	20	5

Thallium	2B	8	8	8
Gold	2B	100	100	1
Palladium	2B	100	10	1
Iridium	2B	100	10	1
Silver	2B	150	10	7
Lithium	3	550	250	25
Antimony	3	1200	90	20
Barium	3	1400	700	300
Molybdenum	3	3000	1500	10
Copper	3	3000	300	30
Tin	3	6000	600	60
Chromium	3	11000	1100	3

ICH guidelines: 2009 saw the release of the first proposal for the management of elemental impurities. This idea acknowledged that elemental contaminant levels were frequently determined by detectability rather than toxicity and that wet chemistry for heavy metals testing was not appropriate. Therefore, it was suggested that new guidelines be developed that take into account both realistic testing considerations and thorough toxicological investigations. The ICH Q3D guidelines were published in December 2014, marking the finalization of the recommendations resulting from these conversations. 24 components are included in the ICH advice, which is divided into 4 groups according to the elements' relative toxicity, chance of occurrence and mode of administration. Based on the toxicological and the mode of administration, exposure limits have also been established to the elements in this class. These data are provided as relevant allowable concentration in drug goods (as μg/g) as well as acceptable daily exposure limits (PDE, in μg).

It is assumed that the maximum dosage will be 10 g per day. The guidelines are meant to help manufacturers determine how much of a risk there is of contamination in the finished goods, which could endanger patient safety. Depending on its class and mode of administration, each element on the list has a unique toxicological profile. The procedure can be made simpler by using this information to highlight which elements must be taken into account as part of the risk assessment and which ones do not. An element needs to be included in the risk assessment if it was added to or used in the production of the pharmaceutical product. In the event that an ingredient is not purposefully added, its inclusion in the assessment is determined by the material's toxicity, its probability of existing and its mode of administration, as indicated in Table 2.

Table 2: ICH classification of elemental impurities.

Elements	**Class**	**If intentionally added (all routes)**	**If not intentionally added**		
			Oral	**Parenteral**	**Inhalation**
Cd	1	Yes	Yes	Yes	Yes
Pb	1	Yes	Yes	Yes	Yes
As	1	Yes	Yes	Yes	Yes
Hg	1	Yes	Yes	Yes	Yes
Co	2A	Yes	Yes	Yes	Yes
V	2A	Yes	Yes	Yes	Yes
Ni	2A	Yes	Yes	Yes	Yes
Tl	2B	Yes	No	No	No
Au	2B	Yes	No	No	No
Pd	2B	Yes	No	No	No
Ir	2B	Yes	No	No	No
Os	2B	Yes	No	No	No
Li	3	Yes	No	Yes	Yes
Sb	3	Yes	No	Yes	Yes
Ba	3	Yes	No	No	Yes
Mo	3	Yes	No	No	Yes
Cu	3	Yes	No	Yes	Yes
Sn	3	Yes	No	No	Yes
Cr	3	Yes	No	No	Yes

United States Pharmacopeia (USP): The USP has general chapters and monographs that describe analytical methods, limitations and elemental impurity control in drug compounds.

Categorization according to USP as shown in Table 3 provides the new classification of metals according to USP (chapters 232 and 233):
Class 1: As, Cd, Hg and Pb: Extremely poisonous across all routes of administration; little to no utility in the production of pharmaceuticals.
Class 2: Toxicity based on the mode of administration.

- **Class 2A:** (Co, V, Ni): Based on the route of administration, a relatively high probability of toxicity.
- **Class 2B:** (Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt): Based on the route of administration, there is a relatively low likelihood of toxicity.

Class 3: (Li, Sb, Ba, Mo, Cu, Sn and Cr): Generally low toxicity (high PDEs) when administered orally, but may need to be taken into account when evaluating the risks associated with parenteral and inhalation routes.

Table 3: USP classification of elemental impurities.

Class	Elements
Class 1	As, Cd, Hg, Pb
Class 2A	Co, V, Ni
Class 2B	Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Ag, Pt
Class 3	Li, Sb, Ba, Mo, Cu, Sn, Cr

USP guidelines
When implementing the elemental impurity regulations, the USP adopted a slightly different strategy, forming working groups to begin the project in 2009. A total of fifteen elements were selected from these working groups, mostly on the basis of their toxicity and probability of occurring. Four elements (As, Cd, Hg and Pb) were required to be tested, while the remaining eleven were optional due to the methods employed. Two chapters, elemental impurities: Limits and elemental impurities: Procedures contained the testing for these elements. These chapters outline the components needed for testing and their corresponding limitations in addition to outlining the methods for preparation, analysis and validation that are necessary for compliance. The original proposal called for these restrictions to become mandatory by December 2012, but due to industry pressure and a desire to align with the ICH recommendations, this deadline was repeatedly pushed back. After extensive industry consultation and the issuance of the ICH Q3D standards, January 2018 has been designated as the final compliance date. The elements were listed in the ICH list, although some of the elements did not have harmonized levels. The last chapters issue is now completely compliant with the ICH Q3D guidelines elements and levels.

European Medicines Agency (EMA): The guidelines for the assessment and management of elemental impurities in medical products are outlined in the EMA's guidance on elemental impurities. According to EMA guidelines, metal wastes are divided into three categories. Class 1 metals are those with substantial toxicities, which include carcinogens for humans. Class 1A, 1B and 1C are the three subclasses that currently comprise the metals contained in class 1. Palladium (Pd) and Platinum (Pt) belong in class 1A. Class 1B elements include Iridium (Ir), Rhodium (Rh), Ruthenium (Ru) and Oxygen (Os). The elements in class 1C are Molybednum (Mo), Vanadium (V), Nickel (Ni) and Chromium (Cr). Class 2 metals include Copper (Cu) and Manganese (Mn), which are considered to be of minor safety concern. Iron (Fe) and Zinc (Zn) are two elements that fall within the class 3 group of metals, which contains those that do not pose a substantial hazard (EMA, 2002; committee for medicinal products for human Use, 2008; European pharmacopoeia, 2009).

European Pharmacopoeia (EP):
Changes to the EP regarding elemental impurities have their roots in a draft document that was submitted in 1998 by the Committee for Medicinal Products for human use (CHMP). In September 2008, this was finally incorporated into European laws, taking effect immediately for new materials and proposing a five-year implementation period for materials already in use. These rules concentrated on residues that could have entered the drug products as a result of catalyst additions (like Pt or Pd) or from wear metals formed during manufacturing from contact with processing equipment, like copper from pipework or stainless steel elements like V and Mo from the processing equipment. Implementations of the elemental impurity regulations within the EP were postponed in order to align with the ICH standards. It was decided to include this document exactly in EP chapter 5.20 (metal catalyst or metal reagent residues) after the ICH guidance was finalized.

CONCLUSION

Summarizing the key findings and emphasizing the critical role of regulatory compliance in ensuring the safety and quality of pharmaceutical products in relation to elemental impurities. This comprehensive review aims to provide a valuable resource for regulatory affairs professionals, researchers and industry stakeholders involved in ensuring the quality and safety of pharmaceutical products in the context of elemental impurities.

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CONFLICT OF INTEREST

The study's authors affirm that there were no financial or commercial ties that might be seen as a potential conflict of interest throughout its execution.

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